

PATENTS

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For: ANTICONVULSANT ENANTIOMERIC
AMINO ACID DERIVATIVES

Dated: February 4, 2003

9
2/5/03
H. Kumar

Assistant Commissioner for Patents
United States Patent and Trademark Office
Washington, D.C. 20231

LETTER

Sir:

The present application is a reissue of U.S. Patent No. 5,773,475. Prior to the submission of the reissue application, applicant had submitted a Certificate of Correction which was approved by the United States Patent and Trademark Office, a copy of which is enclosed herewith. The purpose of this communication is to incorporate the corrections in the Certificate of Correction into the text of the patent.

Applicant is submitting a clean copy of the paragraphs in the patent where errors have been corrected with a Certification of Correction. Since these were made to the application prior to the submission of the reissue application no underlining or bracketing is required. The text written hereinbelow recites the text with the incorporation of the corrections made by the Certificate of Correction.

Please replace the paragraph beginning on Column 2, line 57 with the following:

Research is continuing in this area to find better and more effective anticonvulsant agents, especially for long term treatment (chronic administration). Obviously, the ideal drug is

one that has high pharmacological activity, minimal side effects and is relatively non-toxic and safe to the animal that is being treated. More specifically, the ideal anticonvulsant drug is one that satisfies the following four criteria: (1) has a high anticonvulsant activity, (expressed as a low ED_{50}); (2) has minimal neurological toxicity, (as expressed by the median toxic dose (TD_{50})), relative to its potency; (3) has a maximum protective index (sometimes known as selectivity or margin of safety), which measures the relationship between the doses of a drug required to produce undesired and desired effects, and is measured as the ratio between the median toxic dose and the median effective dose (TD_{50}/ED_{50}); and (4) is relatively safe as measured by the median lethal dose (LD_{50}) relative to its potency and is non-toxic to the animal that is being treated, e.g., it exhibits minimal adverse effects on the remainder of the treated animal, its organs, blood, its bodily functions, etc. even at high concentrations, especially during long term chronic administration of the drug. Thus, for example, it exhibits minimal, i.e., little or no liver toxicity. Although not as critical in short term or acute administration of an anti-convulsant, since the animal may tolerate some low levels of toxicity, the fourth criteria outlined above is extremely important for an anti-convulsant which is to be taken over a long period of time (chronic administration) or in high dosage. It may be the most important factor in determining which anti-convulsant to administer to a patient, especially if chronic dosing is required. Thus, an anti-convulsant agent which has a high anti-convulsant activity, has minimal neurological toxicity and maximal P.I. (protective index) may unfortunately exhibit such toxicities which appear upon repeated high levels of administration. In such an event, acute dosing of the drug may be considered, but it would not be used in a treatment regime which requires chronic administration of the anti-convulsant. In fact, if an anti-convulsant is required for repeated dosing in a long term treatment regime, a physician may prescribe an anti-

convulsant that may have weaker activity relative to a second anti-convulsant, if it exhibits relatively low toxicity to the animal. An anti-convulsant agent which meets all four criteria is very rare.

Please replace the paragraph beginning on Column 7, line 48 with the following:

D Serine (1) is protected with a N-protecting group known in the art, by standard techniques. Thus, for example, it is reacted with carbobenzoxy chloride (CBZ-cl, benzyl chloroformate) generating the N-protected CBZ-D-serine adduct 9. The protected serine adduct is converted to the corresponding ether under Williamson conditions by reacting it with QX wherein Q and X are defined hereinabove (e.g., CH_3I) in the presence of base (e.g., Ag_2O) to form an ether 10. Under these conditions, the acid is also esterified. Subsequent hydrolysis of the ester group in 10 permits amide coupling with ArCH_2NH_2 using amide coupling methodology (e.g., mixed anhydride 1,1' Carbonyldiimidazole) to give the amide 12. Deprotection of the N-protecting group provide the free amine 13 which is then reacted with an acylating agent such as acetic anhydride in base, (e.g., pyridine) to provide the product (R)-8.

Please replace the paragraph beginning on Column 7, line 64 with the following:

If necessary, in any of the procedures described hereinabove, the optical purity of the product may be enhanced by further separation of the S enantiomer from the R enantiomer, by standard techniques known in the art, such as chiral chromatography using a standard chiral support known in the art.

Please replace the paragraph beginning on Column 12, line 39 with the following:

Utilizing the procedure of Example 2(a) with the following amounts of D-serine (5.26 g, 50 mmol), Ac_2O (5.7 mL, 60 mmol), 4-methylmorpholine (11.0 mL, 100 mmol), isobutyl chloroformate (13.0 mL, 100 mmol) and substituting 3-fluorobenzylamine (11.8 mL,

100 mmol) for benzylamine, gave 4.20 g (33%) of the above compound as a white solid after purification: mp 137°-138°C; $[\alpha]_D^{23}$ (c = 1, MeOH) = +20.8°; R_f 0.32 (10% MeOH-CHCl₃); IR (KBr) 3282, 3101, 2944, 1636, 1542, 1252, 1050, 779, 690 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.87 (s, C(O)CH₃), 3.56-3.63 (m, CH₂OH), 4.29 (d, J = 6.0 Hz, CH₂NH), 4.25-4.30 (m, CH), 4.95 (t, J = 5.4 Hz, CH₂OH), 7.00-7.09 (m, 3 ArH), 7.29-7.30 (m, 1 ArH), 7.97 (d, J = 8.1 Hz, NH), 8.44 (t, J = 6.0 Hz, NH), addition of excess (R)-(-)-mandelic acid to a CDCl₃ solution of this product gave only one signal for the acetyl methyl portions; ¹³C NMR (DMSO-d₆) 22.7 (C(O)CH₃), 41.6 (CH₂N), 53.4 (CH), 61.7 (CH₂ OH), 113.3 (d, J_{CF} = 20.0 Hz, (C_{2'} or C_{4'}), 113.6 (d, J_{CF} = 20.7 Hz, C_{2'} or C_{4'}), 122.9 (C_{6'}), 130.1 (d, J_{CF} = 8.2 Hz, C_{5'}), 142.6 (d, J_{CF} = 7.0 Hz, C_{1'}), 162.3 (d, J_{CF} = 241.4 Hz, C_{3'}), 169.6 (C(O)CH₃ or C(O)NH), 170.5 (C(O)CH₃ or C(O)NH) ppm; MS (+Cl) (rel. intensity) 255 (M⁺ + 1, 100); M_r(+Cl) 255.113 54 [M⁺ + 1] (calcd. for C₁₂H₁₆FN₂O₃ 255.114 50); Anal. (C₁₂H₁₅FN₂O₃) C, H, N.

Please replace the paragraph beginning on Column 12, line 66 with the following:

To the product of (a) (2.54 g, 10 mmol) in a stirred CH₃CN solution was successively added Ag₂O (11.59 g, 50 mmol) and MeI (6.2 mL, 100 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 days. The insoluble salts were filtered and the solvent was removed in vacuo to give a white solid which was triturated with Et₂O (100 mL) to give a crude product of the above identified compound. The product was further purified by flash chromatography on SiO₂ gel (10% MeOH-CHCl₃) to give 2.00 g (75%) of the above-identified compound: mp 150°-151°C; $[\alpha]_D^{23}$ (c = 1, MeOH) = +16.5°C; R_f 0.50 (10% MeOH-CHCl₃); IR (KBr) 3287, 3072, 2928, 2883, 1634, 1548, 1256, 1142, 785 cm⁻¹; ¹H NMR (CDCl₃) δ 2.05 (s, C(O)CH₃), 3.40 (s, OCH₃), 3.44-3.47 (m, CHH'OCH₃), 3.81-3.85 (m, CHH'OCH₃), 4.41-4.50 (m, NHCH₂), 4.53-4.59 (m, CH), 6.42 (br s, NH), 6.81 (br s, NH), 6.93-

7.05 (m, 3 PhH), 7.26-7.31 (m, 1 PhH); addition of excess (R)-(-)-mandelic acid to a CDCl_3 solution of the above identified compound gave only one signal for the acetyl methyl protons and ether methyl protons; ^{13}C NMR (DMSO-d_6) 22.8 (C(O)CH_3), 42.7 (CH_2N), 52.6 (CH), 58.9 (OCH_3), 72.0 (CH_2OCH_3), 114.0 (d, $J_{\text{CF}} = 21.5$ Hz, C_2' and C_4'), 122.7 (C_6'), 129.9 (d, $J_{\text{CF}} = 7.7$ Hz, C_5'), 140.6 (d, $J_{\text{CF}} = 6.8$ Hz, C_1'), 162.9 (d, $J_{\text{CF}} = 244.4$ Hz, C_3'), 170.2 (C(O)CH_3 or C(O)NH), 170.5 (C(O)CH_3 or C(O)NH) ppm; MS (+Cl) (rel. intensity) 269 ($\text{M}^+ + 1$, 100); M_r (+Cl) 269.129 31 [$\text{M}^+ + 1$] (calcd for $\text{C}_{13}\text{H}_{18}\text{FN}_2\text{O}_3$ 269.130 15); Anal. ($\text{C}_{13}\text{H}_{17}\text{FN}_2\text{O}_3$) C, H, N.

Please replace the paragraph beginning on Column 13, line 35 with the following:

Utilizing the procedure of Example 2(a) with the following amounts of D-serine (5.26 g, 50 mmol), Ac_2O (5.7 mL, 60 mmol), 4-methylmorpholine (11.0 mL, 100 mmol), and isobutyl chloroformate (13.0 mL, 100 mmol) and substituting 4-fluorobenzylamine (11.8 mL, 100 mmol) for benzylamine, the above-identified compound was prepared as a white solid after purification (4.08 g, 32%); mp: $169^\circ\text{-}170^\circ\text{C}$; $[\alpha]_{\text{D}}^{23}$ ($c = 1$, MeOH) = $+17.6^\circ$; R_f 0.31 (10% MeOH- CHCl_3); IR (KBr) 3289, 3101, 3071, 2936, 1632, 1565, 1543 1508, 1214, 1053, 814 cm^{-1} ; ^1H NMR (DMSO-d_6) δ 1.86 (s, C(O)CH_3), 3.56 (6, $J = 5.4$ Hz, CH_2OH), 4.25 (d, $J = 6.0$ Hz, CH_2NH), 4.25-4.29 (m, CH), 4.91 (t, $J = 5.4$ Hz, CH_2OH), 7.08-7.14 (m, $2\text{C}_2\text{H}$), 7.25-7.29 (m, $2\text{C}_3\text{H}$), 7.93 (d, $J = 7.8$ Hz, NH), 8.39 (d, $J = 6.0$ Hz, NH), addition of excess (R)-(-)-mandelic acid to a CDCl_3 solution of the above-identified compound gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.7 (C(O)CH_3), 41.3 (CH_2N), 55.3 (CH), 61.7 (CH_2OH), 114.8 (d, $J_{\text{CF}} = 21.8$ Hz, 2C_3), 128.9 (d, $J_{\text{CF}} = 8.0$ Hz, 2C_2), 135.6 (C_1), 161.1 (d, $J_{\text{CF}} = 240.1$ Hz, C_4), 169.4 (C(O)CH_3 or C(O)NH), 170.3 (C(O)CH_3 or C(O)NH) ppm; MS (+Cl) (rel. intensity) 255 ($\text{M}^+ + 1$, 100); M_r (+Cl) 255.113 60 [$\text{M}^+ + 1$] (calcd for $\text{C}_{12}\text{H}_{16}\text{FN}_2\text{O}_3$ 255.114 50); Anal. ($\text{C}_{12}\text{H}_{15}\text{FN}_2\text{O}_3 \cdot 0.2\text{H}_2\text{O}$) C, H, N.

Please replace the paragraph beginning on Column 13, line 62 with the following:

Following the procedure of Example 3(b) to the product of Example 4(a) (2.54 g, 10 mmol) in a stirred CH₃CN solution (300 mL) was successively added) Ag₂O (11.59 g, 50 mmol) and MeI (6.2 mL, 100 mmol) at room temperature and then stirred for 7 days. The insoluble salts were filtered, and the solvent was removed in vacuo to given a white solid. The white solid was triturated with Et₂O (100 mL) to give a crude product. The crude product was further purified by flash column chromatography (10% MeOH-CHCl₃) to give 2.00 g (75%) of the above product; mp: 144°-145°C; [α]_D²³ (c = 1, MeOH) = +12.0°; R_f0.52 (10% MeOH-CHCl₃); IR (KBr) 3281, 3102, 3072, 2959, 1632, 1547, 1513, 1223, 1100 cm⁻¹; ¹H NMR (CDCl₃) δ 2.04 (s, C(O)CH₃), 3.38 (s, OCH₃), 3.39-3.46 (m, CHH'OCH₃), 3.80-3.84 (m, CHH'OCH₃), 4.44 (br d, J = 5.4 Hz, CH₂NH), 4.48-4.56 (m, CH), 6.42 (br s, NH) 6.76 (br s, NH), 6.99-7.05 (m, 2 PhH), 7.21-7.31 (m, 2 PhH), addition of excess (R)-(-)-mandelic acid to a CDCl₃ solution of the above-identified product gave only one signal for the acetyl methyl portions and ether methyl portions, ¹³C NMR (CDCl₃) 22.9 (C(O)CH₃), 42.6 (CH₂N), 52.5 (CH), 58.9 (OCH₃), 72.0 (CH₂OCH₃), 115.3 (d, J_{CF} = 22.0 Hz, 2C_{3'}), 129.0 (d, J_{CF} = 6.9 Hz, 2C_{2'}), 133.7 (C_{1'}), 161.9 (d, J_{CF} = 245.3 Hz, C_{4'}), 170.1 (C(O)CH₃ or C(O)NH), 170.4 (C(O)CH₃ or C(O)NH) ppm; MS (+Cl) (rel. intensity) 269 (M⁺ + 1, 100); M_r (+Cl) 269.129 66 [M⁺ + 1] (calcd for C₁₃H₁₈FN₂O₃ 269.130 15); Anal. (C₁₃H₁₇FN₂O₃) C, H, N.

Please replace the paragraph beginning on Column 14, line 28 with the following:

D-Serine (5g) was dissolved in water (85 mL). To this was added MgO (6g), and ethyl ether (40 mL). The mixture was cooled in an ice bath to 0°C. To this ice-cold mixture was added slowly, dropwise benzylchloroformate (95%, 11 mL). Upon complete addition, the

mixture was stirred at 0°C (2h) and then allowed to spontaneously warm to room temperature. Stirring was continued for an additional 30 minutes. The mixture was filtered and the filtrate washed with ethyl ether (2 x 25 mL). The aqueous layer was separated and cooled in an ice bath to 0°C. The pH of this ice-cold aqueous layer was carefully adjusted to 3.0 using 5 N HCl. The acidified solution was stored in a refrigerator overnight. The white crystalline solid product was isolated by filtration, and dried *in vacuo*. The filtrate was extracted with ethylacetate (2 x 50 mL). The combined ethyl acetate extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo* to obtain additional amounts of the white crystalline product. Total product obtained was 7.51 g (68%): mp 118°-120°C.

Please replace the paragraph beginning on Column 14, line 51 with the following:

To a solution of 9 (1.72g, 7.21 mmol) in acetonitrile (150 mL) was added methyl iodide (10.23 g, 72.1 mmol, 4.5 mL) and silver(I)oxide (8.4g, 36 mmol) and the mixture was stirred in the dark at room temperature for 24 hours. The insoluble salts and excess silver oxide were removed by filtration and the filtrate was evaporated *in vacuo* to obtain an oily residue which was subjected to flash column chromatography (silica gel and 5% MeOH-CHCl₃) to obtain pure 10 as a pale yellow oil (1.81g, 94%): R_f (10% MeOH/CHCl₃) 0.75.

Please replace the paragraph beginning on Column 15, line 11 with the following:

A solution of 11 (0.52g, 2.04 mmol) in dry tetrahydrofuran (10 mL) was cooled to -78°C in a dry ice-acetone bath under a N₂ atmosphere. To this was added via a dry syringe 4-methylmorpholine (0.34 mL, 3.06 mmol). After stirring for 5 minutes, isobutyl chloroformate (0.4 mL, 3.06 mmol) was added via dry syringe and then the mixture stirred for 5 minutes. This was followed by the addition of benzylamine (0.32 mL, 3.06 mmol). After stirring at -78°C for 5 minutes, the reaction was allowed to warm to room temperature, and stirring was continued at

room temperature (30 min). The hydrochloride salt of 4-methyl morpholine was removed from the reaction by filtration. The clear filtrate was evaporated *in vacuo* and the residue was triturated with ethyl ether (5.0 mL). The white crystalline product obtained was isolated by filtration after washing with small amounts of ether and air-dried (0.55 g, 78%): mp 112°-114°C, R_f 0.6 (10% MeOH/CHCl₃).

Please replace the paragraph beginning on Column 16, line 33 with the following:

Yield: 1.11 g (46%). mp 139°-142°C. $[\alpha]_D^{23} = 35.3$ (c 2.5, MeOH). ¹H NMR (80 MHz, DMSO-d₆): δ 1.23 (d, J=7.2 Hz, 3H), 1.86 (s, 3H), 4.26-4.35 (m, 1H), 4.29 (d, J=5.8 Hz, 2H), 7.22-7.33 (s, 5H), 8.10 (d, J=7.4 Hz, 1H), 8.42 (t, J=5.8 Hz, 1H).

Please replace the paragraph beginning on Column 16, line 52 with the following:

To a methanolic solution (180 mL) of methyl 2-acetamide-2-methoxyacetate (8.73 g, 54 mmol) was rapidly added benzylamine (8.68 g, 8.80 mL, 81 mmol) and then the mixture was stirred at 50°C (3 days) during which time a beige precipitate appeared. The solvent was removed *in vacuo* and the resulting precipitate was recrystallized from tetrahydrofuran (2X) to give 7.67 g (32%) of the desired product as beige crystals: R_f 0.35 (95:5 chloroform/methanol). mp 145°-146°C.

Please replace the paragraph beginning on Column 16, line 64 with the following:

¹³C NMR (300 MHz, CDCl₃): 23.03 (CH₃CO), 43.51 (CH₂), 55.84 (CH₃O), 78.94 (CH), 127.62 (C₄"), 127.70 (2C₂" or 2C₃"'), 128.70 (2C₂ or 2C₃'), 137.45 (C₁"), 166.91 (COCH₃), 171.57 (CONH) ppm.

Please replace the paragraph beginning on Column 17, line 11 with the following:

Synthesis of Unsubstituted and
Substituted- α -Acetamido-N-benzyl-2-furanacetamides

General Procedure

4-Methylmorpholine (1 equiv) was added to a solution of α -acetamido-2-furanacetic acid (1 equiv) in dry tetrahydrofuran (75 mL/10 mmol) at -10° to -15°C under N_2 . After stirring (2 min.), isobutyl chloroformate (1 equiv) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for 2 additional minutes and then a solution of the substituted benzylamine (1 equiv) in tetrahydrofuran (10 mL/10mmol) was added over 5 min. at -10° to -15°C . The reaction mixture was allowed to stir at room temperature for 5 min. and then the 4-methylmorpholine hydrochloride salt filtered. The organic layer was concentrated in vacuo, and the residue was triturated with ethyl acetate, and the remaining white solid filtered. Concentration of the ethyl acetate layer led to additional amounts of the white solid. The desired product was purified by either recrystallization or flash chromatography of the combined solid material.

Please replace the paragraph beginning on Column 18, line 15 with the following:

To an anhydrous THF solution (400 mL) of methyl- α -acetamido-N-benzylmalonamate (14.4 g, 54.5 mmol) was successively added dry LiCl (4.62 g, 109 mmol), NaBH_4 (4.13 g, 109 mmol) and EtOH (200 mL). The reaction mixture was stirred at room temperature (5h). The suspension was concentration in vacuo. After continuous extraction (12h) of the product using CHCl_3 (1000 mL) and H_2O (250 mL), the organic layer was collected, dried (Na_2SO_4), and removed in vacuo to give a crude white solid. The crude product was triturated with Et_2O (500 mL) to give 11.45 g (89%) of the above compound: mp 201° - 203°C ; R_f 0.40 (10% MeOH- CHCl_3); IR (KBr) 3287, 3085, 2969, 2859, 1648, 1552, 1456, 1055, 697 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.88 (s, $\text{C}(\text{O})\text{CH}_3$), 3.59 (dd, $J = 5.7$ Hz, 5.7 Hz, CH_2O), 4.19-4.35 (m, CH_2NH , CH), 4.92 (t, $J = 5.7$ Hz, OH), 7.10-7.40 (m, 5 PhH), 7.94 (d, $J = 5.7$ Hz, NH), 8.38 (t, J

= 5.7 Hz, NH); ^{13}C NMR (DMSO- d_6) 22.2 (C(O)CH₃), 41.6 (CH₂N), 54.9 (CH), 61.3 (CH₂OH), 126.2 (C_{4'}), 126.5 (2C_{2'} or 2C_{3'}), 127.7 (2C_{2'} or 2C_{3'}), 138.9 (C_{1'}), 169.1 (C(O)CH₃ or C(O)NH), 169.9 (C(O)CH₃ or C(O)NH) ppm; MS (+Cl) (relative intensity) 237 ($M^+ + 1$, 100), 219 (9); $M_r(+Cl)$ 237.123 88 [$M^+ + 1$] (calcd for C₁₂H₁₇N₂O₃ 237.123 92); Anal. (C₁₂H₁₆N₂O₃) C, H, N.

Please replace the paragraph beginning on Column 18, line 42 with the following:

To an CH₃CN solution (500 mL) of the product of Comparative Example 8 (2.36 g, 10 mmol) was successively added Ag₂O (11.59 g, 50.0 mmol) and CH₃I (6.23 mL, 100 mmol) at room temperature and then the reaction mixture was stirred at room temperature (4 d). The insoluble salts were filtered, and the solvent was removed in vacuo to give a white solid. The residue was triturated with Et₂O (50 mL) to give 2.10 g (84%) of the above-identified compound: mp 121°-122°C; R_f 0.47 (10% MeOH-CHCl₃); IR (KBr) 3290, 3087, 2924, 2878, 2820, 1637, 1548, 1139, 695 cm⁻¹; ^1H NMR (CDCl₃) δ 2.04 (s, C(O)CH₃), 3.38 (s, OCH₃), 3.43 (dd, J = 7.8, 9.0 Hz, CHH'OCH₃), 3.82 (dd, J = 4.2, 9.0 Hz, CHH'OCH₃), 4.48 (d, J = 6.0 Hz, NHCH₂), 4.51-4.57 (m, CH), 6.43 (br d, J = 5.4 Hz, NH), 6.74 (br s, NH), 7.25-7.37 (m, 5 PhH); ^{13}C NMR (CDCl₃) 23.2 (C(O)CH₃), 43.5 (CH₂N), 52.4 (CH), 59.1 (OCH₃), 71.7 (CH₂OCH₃), 127.4 (C_{4'} and 2C_{2'} or 2C_{3'}), 128.7 (2C_{2'} or 2C_{3'}), 137.8 (C_{1'}), 170.0 (C(O)CH₃ or C(O)NH), 170.3 (C(O)CH₃ or C(O)NH) ppm; MS (+Cl) (relative intensity) 251 ($M^+ + 1$, 100), 219 (100); $M_r(+Cl)$ 251.139 39 [$M^+ + 1$] (calcd for C₁₃H₁₉N₂O₃ 251.139 57); Anal. (C₁₃H₁₈N₂O₃) C, H, N.

Please replace Table 1 beginning on Columns 21 and 22, line 1 with the following

Table 1:

TABLE 1										
Physical and Pharmacological Data for Functionalized N-Benzyl 2-Acetamidopropionamide Stereoisomers of the formula $ArCH_2NHC(O)CH(R^1)NHC(O)CH_3$										
No.	Stereochem.	R ²	Ar	m p ^a	mice(ip) ^b			rat(po) ^c		
					MES, ^e ED ₅₀	tox, ^d TD ₅₀	PI ₁	MES, ^e ED ₅₀	tox, ^d TD ₅₀	PI ₁
Comp. Ex. 1	(R,S)	CH ₃	Ph	138-139	76.5 [1] (66.6-89.0)	454 [0.5] (417-501)	5.9	48.2 [1] (32.0-71.8)	_h	>20.8
Comp. Ex. 2	(R)	CH ₃	Ph	139-141	54.8 [0.5] (50.3-59.7)	214 [0.5] (148-262)	3.9	28.4 [4] (22.4-35.0)	_h	>35.2
Comp. Ex. 3	(S)	CH ₃	Ph	139-142	548 [0.5] (50.3-59.7)	841 [0.5] (691-954)	1.5	_j	_j	_j
Comp. Ex. 9	(R,S)	CH ₂ OCH ₃	Ph	121-122	8.3 [0.5] (7.9-9.8)	42.9 [0.25] (38.1-46.8)	5.2	3.8 [2] (2.9-5.5)	386.8 [1] (316.0-514.6)	101.8
Ex. 1,2	(R)	CH ₂ OCH ₃	Ph	143-144	4.5 [0.5] (3.7-5.5)	26.8 [0.25] (25.5-28.0)	6.0	3.9 [0.5] (2.6-6.2)	>500 [0.5]	>128.2
Comp. Ex. 11	(S)	CH ₂ OCH ₃	Ph	143-144	>100, <300	>300		>30	>30	_j
Comp. Ex. 8	(R,S)	CH ₂ OH	Ph	201-203	>100, <300	>300		_j	_j	_j
Comp. Ex. 12	(R)	CH ₂ OH	Ph	148-149	53.4 [2] (37.5-67.3)	>500 [2]	>9.4	_j	_j	_j
Ex. 3	(R)	CH ₂ OCH ₃	Ph (m-F)	150-151	6.9 [0.25] (6.1-8.0)	46.3 [0.25] (40.4-54.5)	6.7	6.9 [0.5] (4.3-9.9)	>396 [0.5]	>57.7
Ex. 4	(R)	CH ₂ OCH ₃	Ph (p-F)	144-145	4.2 [0.5] (3.5-5.1)	27.8 [0.25] (22.4-33.5)	6.6	2.6 [2] (1.9-3.6)	>125, <250	_j
Comp. Ex. 4	(R,S)	OCH ₃	Ph	145-146	98.30	>100 <300	>1, <3	_j	_j	_j
Comp. Ex. 6	(R)	furyl	Ph	190-197	3.3	23.8	>.2	_j	_j	_j
Comp. Ex. 7	(S)	furyl	Ph	196-197	>25	>200	_j	_j	_j	_j
Comp. Ex. 5	(R,S)	furyl	Ph	178-179	10.3	~40	>3.9	_j	_j	_j
Comp. Ex. 13	(D,L)	Ph	Ph	112-115	20.3	96.92	4.77	48.3	>1000	>20.7

^a Melting points (°C) are uncorrected.

^b The compounds were administered interperitoneally. ED₅₀ and TD₅₀ values are in mg/kg. Numbers in parentheses are 95% confidence intervals. The dose effect data was obtained at the "time of peak effect" (indicated in hours in the brackets).

^c MES = maximal electroshock seizure test.

^d PI = protective index (TD₅₀/MES ED₅₀)

^e No ataxia observed up to 1000 mg/kg.

^f Tox = neurologic toxicity determined from rotarod test.

^g The compounds were administered orally.

^h Data not available

Please replace the paragraph beginning on Column 23, line 25 with the following:

The following experiments measure the effect of a representative compound of the present invention on the liver. The drug utilized is the compound of Example 1, i.e., R-N-Benzyl-2-Acetamide-3-methoxypropionamide, hereinafter referred to as BAMP.

Please replace Table 3 beginning on Column 26, line 27 with the following Table

3:

TABLE 3

30-DAY RANGE-FINDING ORAL TOXICITY STUDY OF BAMP IN RATS
ORGAN WEIGHT DATA

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; WEEKS=ALL
DEATH=ALL; SUBSET=ALL

LIVER

SEX	DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO	SEX	DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1				RT	F	1				
NUMBER IN GROUP:		10	10	10	10	NUMBER IN GROUP:		10	10	10	10
MEAN:		356.3	11.76	3.323	5.760	MEAN:		202.5	6.56	3.247	3.374
STANDARD DEV:		42.8	1.34	0.350	0.577	STANDARD DEV:		13.1	0.54	0.266	0.296
M	2					F	2				
NUMBER IN GROUP:		10	10	10	10	NUMBER IN GROUP:		10	10	10	10
MEAN:		342.0	11.10	3.248	5.388	MEAN:		214.1	6.91	3.237	3.665
STANDARD DEV:		26.6	0.96	0.161	0.391	STANDARD DEV:		12.2	0.76	0.379	0.440
M	3					F	3				
NUMBER IN GROUP:		10	10	10	10	NUMBER IN GROUP:		10	10	10	10
MEAN:		349.9	11.48	3.278	5.619	MEAN:		207.0	6.71	3.244	3.453
STANDARD DEV:		21.4	1.26	0.265	0.666	STANDARD DEV:		17.7	0.66	0.185	0.350
M	4	100 mg/kg/day x 30 days				F	4				
NUMBER IN GROUP:		10	10	10	10	NUMBER IN GROUP:		10	10	10	10
MEAN:		351.5	11.79	3.351	5.702	MEAN:		218.3	7.88*	3.608	4.179*
STANDARD DEV:		29.3	1.38	0.223	0.725	STANDARD DEV:		18.7	1.00	0.310	0.312
M	5	300 mg/kg/day x 30 days				F	5				
NUMBER IN GROUP:		10	10	10	10	NUMBER IN GROUP:		10	10	10	10
MEAN:		358.8	14.45*	4.016*	7.028*	MEAN:		205.9	7.88*	3.832*	4.313*
STANDARD DEV:		28.4	2.25	0.430	1.141	STANDARD DEV:		14.3	0.88	0.419	0.457

* - Significantly different from control value, $p \leq 0.05$.
RT - Data analyzed following rank transformation.

Please replace the paragraph beginning on Column 29, line 39 with the following:

The 5-day chronic studies in rats demonstrate that 5 daily doses of 48 mg/kg does not induce tolerance to the anticonvulsant effects (MES Test) of Compound A within this period of time. This interpretation is supported by the similar effectiveness of Compound A by the MES test, the increased hexobarbital sleep time, and the unaltered liver microsomal enzyme activity. In view of the increased hexobarbital sleep time in the 5-day treated animals, it was thought important to determine the in vitro effect of Compound A on p-nitroanisole O-demethylase activity. The low inhibitory potency of Compound A ($I_{50} = 5000 \mu\text{M}$) suggests that there is little interference by the compound itself on hexobarbital metabolism in the sleep test. This may indicate that the potentiation of hexobarbital sleep time is central and not peripheral.

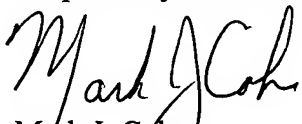
5-day tolerance studies (MES and hexobarbital sleep time tests) and 7-day liver microsomal enzyme studies in rats, indicate that tolerance was not induced by 5 daily doses of the MES ED_{50} (48 mg/kg) of Compound A (4/8 protected in the single dose acute control group; 3/8 protected in the chronically treated group); 5-day chronic treatment increased hexobarbital sleep time from that induced by a single acute dose (31.7 ± 1.7 , 34.3 ± 1.1 , and 44.4 ± 1.9 minutes in solvent control, acute control, and 5-day treated, respectively). There was no significant change in body weight (148.8 ± 5.9 vs 140.0 ± 4.6 g), liver weight (7.71 ± 0.22 vs 7.22 ± 0.45 g), total microsomal protein (32.3 ± 0.56 0.04 nmoles/mg), p-nitroanisole O-demethylase activity (0.50 ± 0.04 vs 0.62 ± 0.07 nmoles/mg/min, NADPH cytochrome c reductase activity (95.3 ± 11.0 vs 105.0 ± 4.1 nmoles/mg/min) in solvent control and 7-day treated, respectively. The candidate

substance (Compound A) had very little inhibitory potency (I_{50} : c.5000 μ M) for in vitro p-nitroanisole demethylation.

It is respectfully submitted that the text hereinabove incorporates only the corrections in the Certificate of Correction into the patent. No new matter has been added to the application.

It is believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Mark J. Cohen', written over the printed name.

Mark J. Cohen

Registration No. 32,211

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
(516) 742-4343

MJC:lf

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,773,475
DATED : June 30, 1998
INVENTOR(S) : Harold Kohn

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 3,

Line 6: "close" should read -- dose --

Column 7,

Line 62: "acctic anhydide" should read -- acetic anhydride --

Lines 66 & 67: "emantiomer" should read -- enantiomer --

Column 12,

Line 58: "C1₁" should read -- C₁ --

Column 13,

Line 11: "62.05" should read -- δ 2.05 --

Line 24: "Mr" should read -- M_r --

Line 26: "H₇" should read -- H₁₇ --

Line 43: "cm⁻" should read -- cm⁻¹ --

Line 53: "2C₃ ." should read -- 2C₃ , --

Column 14,

Line 15: "12.00" should read -- 12.0 --

Line 20: "Mr" should read -- M_r --

Line 40: "was" should read -- was --

Line 51: "actonitrile" should read -- acetonitrile --

Column 15,

Line 11: "tetrahdrofuran" should read -- tetrahydrofuran --

Column 16,

Line 33: "-35.3 -- should read -- = 35.3 --

Line 59: "Rf" should read -- R_f --

Line 66: "2C₃)" should read -- 2C₃)" --

Column 17,

Line 11: "a" should read -- α --

Line 15: "a-acetamido" should read -- α -- acetamido --

Column 18,

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Line 6, Table 1: "24.2" should read -- 48.2"

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Line 28: "Actamide" should read -- Acetamide --

Column 26,

Line 60, Table 3: "2.24" should read -- 2.25 --

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Line 26, Table 3: "Date" should read -- Data --

Column 29,

Line 53: "5-day tolerance..." should begin a new paragraph.
Line 57: "group; protected" should read -- group; 3/8 protected --



Attest:

Brenda Moore

Attesting Officer

Signed and Sealed this

Twenty-seventh Day of November, 2001

Nicholas P. Godici

NICHOLAS P. GODICI

Acting Director of the United States Patent and Trademark Office

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It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

On the Title Page, after Section [54], insert the following:

--"This invention was made with Government support under Grant/Contract
No. NIH NS 15604 awarded by the National Institutes of Health.
The Government has certain rights in the invention."--

MAILING ADDRESS OF SENDER:

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
(516) 742-4343

PATENT NO. 5,773,475

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jc825 U.S. PTO
10/058634
01/28/02



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